WEB Table 1: DIDP Developmental Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Number[a]	Dose*	Maternal effects	Fetal effects
Sprague-Dawley Rat Waterman et al. 1999 (*2*)	Prenatal developmental toxicity study. DIDP administered in oil by gavage on gd 6–15. Sacrificed on gd 21. Dams weighed on gd 0, 6, 9, 12, 15, 18, and 21. Maternal uterus and ovaries were weighed, corpora lutea were counted and implantation sites examined. Fetuses were weighed, sexed, and examined for gross external malformations. Half of the fetuses were examined for visceral malformations and the other half for skeletal malformations.	25 22 24 24	0 100 500 1,000	 NOAEL ↓ Weight gain. ↓ Food Intake.	 NOAEL[b] ↑ % Fetuses with cervical ribs (6.2 vs 1%). ↑ % Fetuses with lumbar ribs (21.2 vs 8.2%). ↑ % Litters with cervical ribs (41.7 vs 8%). ↑ % Litters with lumbar ribs (95.8 vs 40%). ↑ % Fetuses with cervical ribs (9.2 vs 1.0%). ↑ Fetuses with lumbar ribs (52 vs 8.2%).

*Dose measured in mg/kg/bw/day.
[a]Number of litters examined.
[b]NOAEL selected by Expert Panel is lower than study author's selection.

NE=No Effect
↑=Statistically Significant Increase
↓=Statistically Significant Decrease

WEB Table 2: DIDP Developmental Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Number[a]	Dose*	Maternal Effects	Fetal Effects
Wistar Rat Hellwig et al. 1997 (*1*)	Prenatal developmental toxicity study. DIDP administered in oil by gavage on gd 6–15. Dams weighed on gd 0, 6, 10, 15, and 20 and sacrificed on gd 20**.** Maternal uteri were weighed, corpora lutea were counted and implantation sites examined. Fetuses were weighed and examined for gross external malformations. Half of the fetuses were examined for visceral malformations and the other half for skeletal malformations.	10 8 7 10	0 40 200 1,000	 NE NOAEL ↑Liver to body weight ratios. Vaginal hemorrhage in 3 dams. ↓Food intake.	 NOAEL[b] ↑Fetuses/litter with variations (38 vs 24%). ↑Fetuses/litter with variations (44 vs 24%). ↑Cervical ribs (15 fetuses in 6 litters vs 1 fetuses). ↑14th ribs (21 fetuses in 8 litters vs 1 fetus).

*Dose measured in mg/kg/bw/day.
[a]Number of litters examined.
[b]NOAEL selected by Expert Panel is lower than study author's selection.

↑=Statistically Significant Increase
↓= Statistically Significant Decrease

Table WEB-3: DIDP Reproductive Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Number[a]	Dose*	Parental Effects**	Offspring Effects**
Crl:CDBR, VAF Plus Rats Exxon Biomedical 1997 (*3*)	Two-generation reproductive toxicity study. DIDP administered in feed for 10 weeks prior to mating at levels of 0, 0.2, 0.4, and 0.8%. Males treated through mating period and females through gestation and lactation. Body weight and food intake was measured weekly. Estrous cycles were evaluated. F_0 dams were killed at the end of lactation and males were killed following birth of last litter. Reproductive and other key organs were examined histologically. Primordial oocytes were counted in females and sperm was evaluated in males. Details of the second generation breeding experiment are listed on the next page.	40 30 30 40	0 103–198 / 127–203 / 131–149 / 172–361 211–405 / 253–416 / 262–287 / 359–734 427–781 / 508–775 / 524–551 / 641–1,582	↓Normal sperm in F_0 (<1.4%). ↑Liver hypertrophy in F_0. ↑Kidney to body weight ratio in F_0 males. ↓Normal sperm in F_0 (<1.4%). ↑Epididymis to body weight ratio in F_0. ↑Liver to body weight ratio with hypertrophy in F_0. ↑Kidney to body weight ratio in F_0. ↑Stomach lesions in F_0 females. No effects on F_0 mating, fertility, fecundity, or gestational indices, no reproductive organ lesions, and no effect on oocyte or sperm counts at any dose. ↓Normal sperm in F_0 (<1.4%). ↓Estrous cycle length in F_0. ↓Ovary to body weight ratio in F_0. ↑ Epididymis and testes to body weight ratio in F_0. ↓Weight gain in F_0 during lactation. ↑Liver to body weight ratio with hypertrophy in F_0. ↑Kidney to body weight ratio in F_0 with histological changes in males. ↑Stomach lesions and thymus atrophy in F_0 females.	 ↑Liver to body weight ratio (F) with hypertrophy in F_1. Delayed vaginal opening in F_1 (33.5 vs 32.2 days). ↓F_1 pup birthweight. ↓F_1 pup survival at birth and pnd 4. ↑Liver to body weight ratio with hypertrophy in F_1. Delayed vaginal opening in F_1 (34.2 vs 32.2 days).

[a]Number of breeding pairs.

*Doses (in mg/kg bw/day) for: Males during premating / females during premating / females during gestational period / females during lactational period.

**Parental effects are discussed in Section 4 and offspring effects in Section 3.

↑=Statistically Significant Increase

↓=Statistically Significant Decrease

Table WEB-3 (cont): DIDP Reproductive Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Number[a]	Dose*	Parental Effects**	Offspring Effects**
Crl:CDBR, VAF Plus Rats Exxon Biomedical 1997 (*3*)	Sexual maturation was monitored in F_1 pups selected for second generation breeding. Upon weaning the pups were fed diets with the same DIDP concentrations as parental rats. The same parameters examined in the F_0 rats were examined in the F_1 rats.	30	0		
		30	117–216 / 135–218 / 135–152 / 162–379	↑Liver to body weight ratio (F). ↑Hypertrophy in F_1. ↑Kidney to body weight ratio in F_1 (M).	↓F_2 pup survival on pnd 1 and 4.
		30	229–437 / 273–433 / 262–297 / 334–761	↑Epididymis and seminal vesicles to body weight ratio in F_1. ↑Liver to body weight ratio in F_1 with hypertrophy. ↑Kidney to body weight ratio in F_1.	↓F_2 pup survival on pnd 1 and 4. ↑Liver hypertrophy in F_2 pups.
		30	494–929/ 566–927 / 574–611 / 637–1424	No effects on F_1 mating, fertility, fecundity, or gestational indices, no reproductive organ lesions, and no effect on oocyte or sperm counts at any dose. ↑Epididymis, seminal vesicle, and testes to body weight ratio in F_1. ↓Weight gain in F_1 during lactation. ↑Liver to body weight ratio with hypertrophy in F_1. ↑Kidney to body weight ratio in F_1 with histological changes in males. ↑Thymus atrophy in F_1 females.	↓F_2 pup birthweight. ↓F_2 pup survival on pnd 1, 4, 7 and at weaning. Undescended testes in 4 pups. ↑Liver hypertrophy in F_2 pups.

[a]Number of breeding pairs.

*Doses in mg/kg bw/day for: Males during premating / females during premating / females during gestational period / females during lactational period.

**Parental effects are discussed in Section 4 and offspring effects in Section 3.

↑=Statistically Significant Increase

↓=Statistically Significant Decrease

Table WEB-4: DIDP Reproductive Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Number[a]	Dose*	Parental Effects**	Offspring Effects**
Crl:CDBR, VAF Plus Rats Exxon Biomedical 2000 (*4*)	Two-generation reproductive toxicity study. DIDP administered in feed for 10 weeks prior to mating at levels of 0, 0.02, 0.06, 0.2, and 0.4%. Males treated through mating period and females through gestation and lactation. Body weight and food intake were measured weekly. F_0 dams were killed and necropsied at the end of lactation and males were killed and necropsied after mating. Pups were examined for survival and sexual maturation. One pup/sex/litter was necropsied at pnd 21. Histological examinations were not conducted. Details of the second generation breeding experiment are listed on the next page.	30 30 30 30 30	0 12–23 / 14–21/ 13–15 / 19–37 33–68 / 40–58 / 39–43 / 57–112 114–225 / 139–202 / 127–147 / 178–377 233–453 / 274–406 / 254–295 / 356–744	NE NE NE ↑Liver and kidney to body weight ratio. No effects on mating, fertility, fecundity, or gestational indices at any dose.	NE NE NE No effects on survival, body weight gain, organ weights, anogenital distance, nipple retention, preputial separation, vaginal opening, or malformations.

[a]Number of breeding pairs.
*Doses in mg/kg bw/day for: Males during premating / females during premating / females during gestational period / females during lactational period.
**Parental effects are discussed in Section 4 and offspring effects in Section 3.

↑=Statistically Significant Increase
NE=No Effect

Table WEB-4 (cont): DIDP Reproductive Toxicity, Rats

Species, Strain, and Source	Experimental Regimen	Number[a]	Dose*	Parental Effects**	Offspring Effects**
Crl:CDBR, VAF Plus Rats Exxon Biomedical 2000 (*4*)	Upon weaning the pups were fed diets with the same DIDP concentrations as parental rats. The remaining details are as described for the 1st generation.	30 39 30 30 30	0 32 / 32 / 11–26 / 14–25 / 13–15 / 19–40 94 / 95/ 33–76 / 41–77 / 38–44 / 52–114 313 / 313 / 114–254 / 137–266 / 134–151 / 166–352 635 / 645 / 235–516 / 271–524 / 256–286 / 356–747	 NE NE ↑Kidney to body weight ratio in (M). ↑Liver to body weight ratio (F). ↑Kidney to body weight ratio (M). ↑Liver to body weight ratio. No effects on mating, fertility, fecundity, and gestational indices at any dose.	 NE NE ↓Pup survival on pnd 1 and 4. ↓ Pup body weight on pnd 14 (F) and pnd 35(M). ↓Pup survival on pnd 1 and 4. ↓ Pup body weight on pnd 14 , pnd 21 (F), pnd 28 (M), and pnd 35(M). ↑Liver to body weight ratio (F). ↑Age of preputial separation (+1.2 days). No effects on anogenital distance, nipple retention, or vaginal opening, and no malformations.

[a]Number of breeding pairs.
*Doses (in mg/kg bw/day) for: Males during first two weeks post weaning / females during first two weeks post weaning / males during premating / females during premating / females during gestational period / females during lactational period.
**Parental effects are discussed under Section 4 and offspring effects under Section 3.

NE=No Effect
↑=Statistically Significant Increase

References:

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3. Exxon Biomedical Sciences Incorporated. Two generation reproduction toxicity study in rats with di-isodecyl phthalate (DIDP; MRD-94-775). East Millstone, NJ: Exxon Chemical Company; Exxon Chemical Europe, Inc., 1997.
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